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NOVEL THERAPEUTIC AGENTS THAT MODULATE ENZYMATIC PROCESSES
NOUVEAUX AGENTS THERAPEUTIQUES MODULANT LES PROCESSUS ENZYMATIQUES

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English Abstract

Novel multi-binding compounds are disclosed that modulate enzymatic processes. The compounds of the invention comprise from 2-10 ligands covalently connected, each of said ligands being capable of binding to an enzyme, enzyme substrate or enzyme cofactor thereby modulating the biological processes/functions thereof.

French Abstract

L'invention porte sur de nouveaux composés multi-liants modulant les processus enzymatiques. Lesdits composés comportent de 2-10 ligands unis par covalence dont chacun peut se fixer à une enzyme, à un substrat d'enzyme ou à un cofacteur d'enzyme et modifier par là leurs processus et fonctions biologiques.

Fulltext Availability:

Detailed Description
Claims

Detailed Description

... effects.

Other examples of diseases in which enzymes are involved include infectious diseases caused by **bacteria**, protozoa or fungi, viral diseases such as AIDS (e.g., reverse transcriptase or protease enzymes... rasagiline, 1370U, L-650477, indeloxazine, Alzheimer's disease moclobemide, brofaromine, EXP-631 Neurodegenerative disease Dementia

Dihydrofolate reductase Cancer Methotrexate., edattexate. piritrexim, LY LY-316373, (1 1.3) Psoriasis 1954U89, E-34335, AG...tumor Uterine cervix tumor Bladder tumor Urinary tract tumor Renal tumor

17

Ribosomal protein biosynthesis **Bacterial** infection Chloramphenicol, erythromycin, clarithromycin, azithromycin, (50S ribosomal subunit) Pneumocystis carinii infection dirithromycin, flurithromycin clindamycin, lincomycin **bacteria**] Tetracycline, chlortetracycline, oxytetracycline, demeclocycline, (Aminoacyl tRNA site on 30S

methacycline, doxycycline, minocycline, CL-331002, ribosomal...

...CL-331928, CL-344667, CL-329998, PAM-MINQ
 (2 2.12)
 Ribosomal protein biosynthesis Anti- **bacterial** Streptomycin, gentamicin, tobramycin, amikacin, netilmicin, (30S subunit) kanamycin, neomycin, spectinomycin, dactimicin, paromomycin,
 (2 2.12) trospectornycin
 Ribosomal protein biosynthesis Anti- **bacterial** Fusidic acid, purpuromycin
 (soluble protein factors)
 (2 2.12)
 Glucan synthase Fungal infection LY-303366...

...H)-one,
 COP-5241 1. RG-8803, BP SU-6668
 Beta subunit of DNA-dependant **Bacterial** infection Rifampin. rifabutin, rifalazil, T9, SPA-S-565
 RNA polymerase
 (2 7.6)
 DNA polymerase...A-502 I 1. SPV-30, VF-1 618, TNK-651
 19
 D,D-transpeptidases **Bacterial** infection Beta-lactams
 (PBP 2a.- 2b) Penicillin G, penicillin V, methicillin. nakillin. oxacillin.
 cloxacillin, dicloxacillin...

...meziocillin, piperacillin,
 (PBP 1a) cephalothin, cefazolin, cephalixin. cefadroxil, cefamandole, cefoxitin, cefaclor, cefuroxime, loracarbefcefonid, D,D- **Carboxypeptidase** cefotetan, ceforanide. cefotaxime. cefpodoximc proxetil,
 (PBP 3-7) ceftizoxime, ceftriaxone, ccfoprazone, ceftazidime, cefepime, (3 16...CH-263, marimastat analogs
 (3 24) Inflammatory bowel disease
 Rheumatoid arthritis
 Ulcerative colitis
 Beta-Lactamase **Bacterial** infections Clavulanic acid, sulbactam. tazobactam. Ro 0480, HM-3030, (3 2.6) GD40, Ro48-8724...

...186195, DWC-751,2085-P, CP
 72436, BK-218, BRL42715, SB-223328, Ro 1317
 Undecaprenyldiphosphatase **Bacterial** infections Bacitracin
 (3 1.27)
 H+/K+ ATPase Peptic ulcer Omeprazole, leminoprazole, rabeprazole, equalen, SKF...

...34655, Ro 5364, T-776, nicotinamide
 Gastrointestinal disease derivatives, pantoprazole, lansoprazole, SKF-96067, SPI-1447,
Bacterial infection AD-9161, YJA-20379, A-28200, SKF-96356, YM-020, Fungal infection bafilornycin A derivatives, atractylon, saviprazole, OPC-22575
 Parasite infection
 Isomerase Enzymes
 21
 DNA gyrase **Bacterial** infections Nalidixic acid. norfloxacin, ofloxacin, ciprofloxacin, cinoxacin, (5 1.3)- Fungal infections sparfloxacin, lomefloxacin, fleroxacin...NSAIDs) including aspirin, indomethacin, ibuprofen, and naproxen. A fourth example of an oxidoreductase enzyme is **dihydrofolate reductase** (DHFR), which catalyzes the conversion of dihydrofolate polyglutamate to tetrahydrofolate polyglutamate ...is selectively inhibited by the antibacterial agent rifampin. In a third example, protein biosynthesis in **bacterial** cells is selectively inhibited by a variety of antibiotics (including gentamicin and other aminoglycosides, tetracycline...

...transglycosylase responsible for the glycosyl transferase reaction which incorporates lipid intermediate 11 into the growing **bacterial** cell wall. Vancomycin acts via a substrate sequestration mechanism; i.e., it binds to and...

...the action of a series of penicillin binding proteins (PBPs), most notably multifunctional, membrane-bound **transpeptidase** enzymes that are responsible for cross-linking of the **bacterial** cell wall.

3. Hydrolase enzymes mediate particular subsets of transfer reactions in which moieties are...

...which is then available for reuse as the lipid carrier for intermediates 27 involved in **bacterial** cell wall biosynthesis. The topical antibacterial agent bacitracin inhibits the diphosphatase process by sequestering the ...dazoxiben and pirmagrel. A third example of an isomerase is alanine racemase, a soluble, monomeric **bacterial** enzyme that produces D-alanine for incorporation into the cell wall. A fourth example of...

...agents, in particular the quinolones, which inhibit the alpha2beta2 tetrameric topoisomerase II (DNA gyrase) in, **bacterial** cells, and also etoposide, and teniposide, which inhibit the mammalian topoisomerase 11 enzyme.

6. Ligase...

...mediates the ATP-dependent condensation of two D-alanine subunits as an early step in **bacterial** cell wall biosynthesis.

Nearly all known enzymes are proteins. As is true for all proteins... disease states include, but are not limited to, treatment of a mammal afflicted with pathogenic **bacteria**, in particular staphylococci (methicillin sensitive and ...to inhibit gastric acid secretion as described in U.S.

Patent 4,255,43 1.

Dihydrofolate reductase
 Anti-leukemia activity is monitored using L 1 21 0 leukemia according to the method...and Carboxyl Groups
 Bacitracin is an antibacterial antibiotic that inhibits an enzymatic process involved in **bacterial** cell wall biosynthesis. Bacitracin is a widely utilized animal growth promoter and an important component...

...antibacterial ointments. Bacitracin is effective against a subset of both Gram-positive and Gram-negative **bacteria** in vitro, and it has recently shown promising activity against vancomycin-resistant *Enterococcus faecium* in...isocarboxazid tranvicypromine. selegifine
 (1 3.6) Depression
 Dihydrofolate reductase Anti-parasite Chloroguanide. pyrimethamine (microbial) Anti- **bacterial** Trimethoprim
 (1 1.3)
 Dihydrofolate reductase Monomer Anti-cancer levolethotrexate
 (1 1.3) Psoriasis
 Trypanothione **Dihydrofolate reductase** In vitro Synthetic analogues of trimethoprim were tested
 %4 inhibitory effects on protozoan and mammalian
 in **dihydrofolate reductase** using standard analytical methods
 Fn
 CD
 6-Phosphogluconate In vitro Inhibitors of enzyme activity tested...that bind
 M 80
 tD (PBP 1-6) PBPs and block cell wall synthesis by **bacteria**, were studied

r

M

Transglycosylase In vitro The inhibition of cell wass synthesis was
studiec...

...of dihydropteroate synthase by
sulfanilamides with 3',5'-halogen substitutions
Fn evaluated

CD

D,D- **carboxypeptidase** in vitro Inhibition of enzyme, expressed by
Ochrobactru

(PBP 3-7) anthropi studied

Table 2...racemase In vitro Inactivators of alanine racemase were
evaluated

cultures of Gram positive and negative **bacteria**

M

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U)

I Prostacyclin synthase In vitro The effect of enzyme inhibition on...

...effects of inhibitors of cylcas
were tested

DNA gyrases In vitro Effect of inhibitors, of **bacterial** gyrases, was
studied in vitro using time-kill assays 39(12):282

Topoisomerase 11 In...

Claim

... the enzyme is acrosin, the figand cannot be a benzamidine;
when the enzyme is a **bacterial** transglycosylase, the figand cannot be a
glycopeptide; when the enzyme is **bacterial** DNA gyrase, the figand
cannot be a quinolone;
when the enzyme is thrombin, the ligand...claim 12, wherein the method is
chosen from treatment of a mammal afflicted with pathogenic **bacteria** ,
psoriasis, multiple sclerosis, rheumatoid arthritis, insulindependent
diabetes, breast cancer and prostate cancer, disease states related...

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